Controlling the Release of Small, Bioactive Proteins via Dual Mechanisms with Therapeutic Potential.

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Public Summary:
Injectable delivery systems that respond to biologically relevant stimuli present an attractive strategy for tailorable drug release. In this manuscript we report the creation of hydrogels that are formed in situ and degrade in response to clinically relevant endogenous and exogenous stimuli, specifically reducing microenvironments and externally applied light. These types of hydrogels can have broad applications in regenerative medicine as they can be loaded with proteins such as growth factors and cytokines, which can stimulate the growth of tissue.

Scientific Abstract:
Injectable delivery systems that respond to biologically relevant stimuli present an attractive strategy for tailorable drug release. Here, the design and synthesis of unique polymers are reported for the creation of hydrogels that are formed in situ and degrade in response to clinically relevant endogenous and exogenous stimuli, specifically reducing microenvironments and externally applied light. Hydrogels are formed with polyethylene glycol and heparin-based polymers using a Michael-type addition reaction. The resulting hydrogels are investigated for the local controlled release of low molecular weight proteins (e.g., growth factors and cytokines), which are of interest for regulating various cellular functions and fates in vivo yet remain difficult to deliver. Incorporation of reduction-sensitive linkages and light-degradable linkages affords significant changes in the release profiles of fibroblast growth factor-2 (FGF-2) in the presence of the reducing agent glutathione or light, respectively. The bioactivity of the released FGF-2 is comparable to pristine FGF-2, indicating the ability of these hydrogels to retain the bioactivity of cargo molecules during encapsulation and release. Further, in vivo studies demonstrate degradation-mediated release of FGF-2. Overall, our studies demonstrate the potential of these unique stimuli-responsive chemistries for controlling the local release of low molecular weight proteins in response to clinically relevant stimuli.